that the term implies more than what is being positively recited. Applicants respond that in each claim, the term "generalized" is used only in reference to the structural formula, which is in fact a generalized structural formula. It is therefore descriptive of the formula, and should not be objectionable. Nevertheless, the term "generalized" has been deleted from the claims in which it was used.

In paragraph 2, the examiner states that the language "wherein binding is achieved via the terminal carbon atoms" in claims 1-3, 7-9, and 13-15 renders these claims indefinite, because "binding" is not synonymous with "bonding", and because the examiner maintains that R^1 and R^2 are not defined properly to indicate that they have terminal carbon atoms. In response, applicants have amended the claims to replace "binding" with "bonding". With respect to the examiner's second point, however, applicants respond that the claim language permitting R^1 and R^2 together to constitute a bridge is perfectly clear, and should be acceptable. In each claim, the groups R^1 and R^2 are shown bonded to the central ring in the main structural formula, and below this, it is stated "wherein R^1 and R^2 : .....together form a bridge of structure (partial structure given) wherein .... bonding is achieved via the terminal ..... atoms". The partial structures representing R^1 and R^2 together are defined as bridges, and as drawn, clearly show ends which are the terminal atoms of the respective bridges; if there were any doubt, the claim language further makes clear that the bridges are bonded to the central ring of the main structural formula via their terminal atoms, thus forming a fused ring.

If the examiner would prefer, the applicants could amend the partial structural formulae of the R^1/R^2 bridges to indicate in these partial structures the location of the bonds from the bridges to the central ring, such as in the following exemplary partial structures:
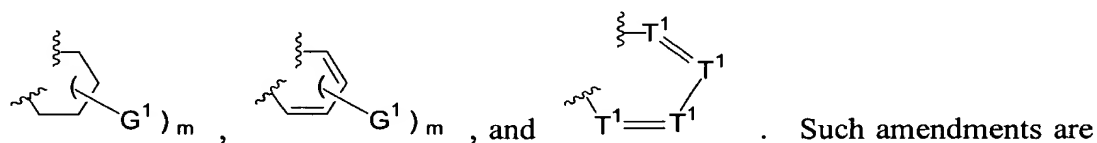
. Such amendments are deemed to be unnecessary, however.

In paragraph 3 of the official action, the examiner rejects claims 1-3, 7-9, and 13-15 for use of the word "containing", which he maintains renders the claims indefinite as being open-ended and synonymous with "including", etc. Applicants respond that a proper reading of the claim language will show that in each case, the word "containing" is

used either to refer to the lower ring in the main structural formula for identification purposes, or to explain that when two groups R^6 are located on the same nitrogen atom and may be linked by a bond, an O, an S, or an N bearing an R^3 group, then a "N-containing heterocycle of 5-7 ring atoms" is formed. In the first usage, the language is clear in identifying the lower ring of the main structural formula. In the second usage, the language is clear in defining that in certain recited circumstances, the resulting heterocycle will contain at least one N atom. Applicants have amended the claims to delete the language "N-containing" as used in the second sense, on the ground that it is superfluous, not because the examiner is correct in his rejection. As used herein, the word "containing" is not open-ended as the examiner asserts.

In paragraph 4 of the official action, the examiner rejected claims 6, 12, and 18 for use of the term "including". In paragraph 5, claims 5, 11, and 17 were rejected for use of the language "abnormal angiogenesis". In response, the applicants have amended claims 5, 11, and 17 to delete the language "characterized by abnormal angiogenesis or hyperpermiability processes" and insert a recitation of the general conditions to be treated, and have written new claims 20-25 to claim the particular conditions previously recited after the term "including" in claims 6, 12, and 18, and have cancelled claims 6, 12, and 18.

In paragraph 6, the examiner rejected claim 19 on the ground that species u) is outside the scope of the elected subject matter. Species u) has now been deleted from claim 19.

Rejections under §112, first paragraph

On pages 4-7 of the official action, the examiner rejected claims 5-6, 11-12, and 17-18 as lacking enablement, for use of the language "abnormal angiogenesis", which he maintains reads on numerous conditions, some yet to be discovered. The examiner states that "it is recited that the instant compounds are therefore useful in treating any or all conditions, for which the applicants provide no competent evidence." This is not true. Nowhere in the application or claims do the applicants recite that the compounds of the invention are useful in treating any or all conditions.

The applicants disclose and claim treating conditions which have been linked in the scientific literature to deregulated VEGF expression. They believe that where scientific studies have established connections between inhibition of a certain biochemical

60

pathway and a variety of medical conditions, then it is reasonable and appropriate to claim treatments of those conditions by administering an inhibitor of that pathway.

The applicants have cited on pages 2 and 3 of the specification many references showing that deregulated VEGF expression contributes to the development of a number of diseases that are characterized by abnormal angiogenesis. References are cited, for example, which show a connection between tumor growth and an upregulation of the VEGF/KDR pathway. The connection between activation of VEGF receptor kinases such as KDR and blood vessel formation (angiogenesis) is well documented and generally accepted by the scientific community. The applicants also cite references which correlate the "abnormal" hyperproliferation of blood vessels with various eye diseases resulting in loss of quality of life, eventually resulting in blindness. A reference linking high VEGF levels and degenerative joint disease (arthritis) is given at the top of page 3 along with a reference in which an angiogenesis inhibitor was shown to prevent neovascularization of the joint in the rat collagen arthritis model (a recognized model of rheumatoid arthritis). Yet another paragraph gives a reference to increased VEGF expression in various cited skin disorders including psoriasis. It would be clear to one skilled in the art that these and other diseases marked by elevated VEGF/KDR levels have the potential to be mediated by KDR kinase inhibitors such as the claimed substances.

That a given disease is "difficult to treat" or "there is no known drug" is not a compelling reason to reject claims based on a reasonable scientific hypothesis (supported by literature references) that inhibition of a biological pathway can inhibit or reverse the progression of the disease. One should not have to show by human clinical evidence that a given new drug (or any drug acting by the same mechanism) has been successful in the treatment of a disease before a patent is granted on that new material. The applicants have presented a reasonable scientific hypothesis and have supported it by credible literature references. Many other articles exist in peer review journals, in addition to those cited in this application, that link KDR activation, angiogenesis, and arthritis or psoriasis.

It is deemed that with the cancellation of claims 6, 12,and 18, the amendment of claims 5, 11, and 17 to recite the conditions to be treated, and the writing of new claims 20-25 to recite certain of these conditions more particularly, the examiner's concerns with respect to enablement have now been addressed.

Rejection under §102

On page 8 of the official action, the examiner rejects claims 1-19 as anticipated by Bold (US 6,258,812). This rejection is improper, as the examiner has not identified a single compound disclosed in the '812 reference which falls within the present claims.

Recitation of certain areas of overlap between the disclosure of a reference and claims of a patent application is not sufficient for an anticipation rejection. For a proper rejection of a claim to chemical compounds on grounds of anticipation, the examiner must show that the rejected claim reads on a compound disclosed by the cited reference in satisfaction of §112 such that the prior art compound is properly in the possession of the public.

It appears that the examiner in this application does not understand the claim structure employed here. The first paragraph of the SUMMARY (bottom of page 3 – top of page 4) explains that the compounds on the invention are broadly claimed using a set of three overlapping generic claims, which differ from each other somewhat. These are claims 1, 7, and 13. Claims 2 and 3 are narrower statements of the subject matter of claim 1; claims 8 and 9 are narrower statements of the subject matter of claim 7; and claims 14 and 15 are narrower statements of the subject matter of claim 13. Claims 1-3, 7-9, and 13-15 have different points of novelty relative to the art. In claims 1-3, the group Y provides novelty. In claims 7-9, the substituents G^3 on the lower ring of the general structure provide novelty. In claims 13-15, the substituents G^4 on the upper ring of the general structure provide novelty.

Rejection under §103

On page 9 of the official action, the examiner rejected claims 1-19 as being obvious over Bold '812.

The examiner states "The instant claims differ from the reference in requiring variously substituted compounds with substituents in the phthalazine ring, heterocyclic ring A-B-D-E-L ring, and J ring. Furthermore, claim 19 requires specific species. Bold et al. as noted in examples shown on col. 34-81 teaches variously substituted phthalazines but not all claimed in the instant claims. However, Bold et al. teaches the equivalency of exemplified substituted phthalazines shown in examples and the tables stated above with phthalazines with variously substituted in aryl ring, N-A-B-D-E ring and the aryl ring of

the phthalazine ring claimed in the definition of compound of formula I. See cols. 1 through col. 17. Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made would have been to make compounds variously substituted phthalazine and aryl and N-A-B-D-E rings as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.
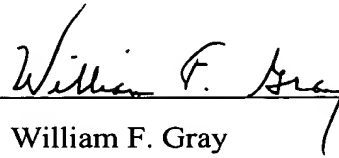
The applicants respond as follows. First, this rejection is a jumble and difficult to understand. Second, both the instant claims and the reference require variously substituted compounds with substituents on the central ring, top ring, and bottom ring (as shown in the structural formulae) and this cannot by itself make the claimed compounds obvious. Third, the fact that claim 19 claims species does not make those species obvious in light of the reference. Fourth, the reference does not teach any of the presently claimed compounds (contrary to the examiner's implied conclusion otherwise). Fifth, simply because the reference arguably teaches that variously substituted phthalazines there disclosed and claimed are equivalent in their utilities does not make all other variously substituted phthalazines obvious.

This rejection is improper because the examiner has not properly pointed out the differences between the compounds of present claims 1, 7, and 13, respectively, and the compounds disclosed in the reference which the examiner believes make the presently claimed compounds obvious. Furthermore, he has not explained why one of ordinary skill in the art would be motivated to make the alterations to the reference compounds which would be necessary to convert any of them into any of the claimed compounds. A broad-brush conclusory obviousness rejection such as that made here is contrary to US case law.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

In view of the above amendments and arguments, this application is deemed to be in condition for allowance, and allowance is accordingly requested.

Respectfully submitted,

William F. Gray

Reg. No. 31018

Phone: (203) 812-2712

Date: _24 Aug 02_

Bayer Corporation
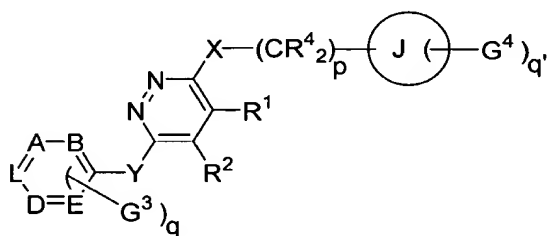
400 Morgan Lane

West Haven, CT 06516-4175

Version with markings to show changes made:

In the claims:

Claims 6, 12, and 18 have been cancelled, but are shown in the list below for the convenience of the examiner.

Claims 1-3, 5, 7-9, 11, 13-15, 17, and 19 have been amended as shown below.

Unamended claims 4, 10, and 16 as well as new claims 20-25 are shown in the list below for the convenience of the examiner.

1. (amended) A compound having the [generalized] structural formula

$$X-(CR^4{}_2)_p-(J)-G^4{}_{q'}$$
$$N-N,\ Y,\ R^1,\ R^2$$
$$A-B,\ L,\ D=E,\ G^3{}_q$$

wherein

R^1 and R^2 :

i) independently represent H or lower alkyl;

ii) together form a bridge of structure

$$-/\!\!\!\diagdown G^1{}_{)m}$$

wherein [binding] bonding is achieved via the terminal carbon atoms;

iii) together form a bridge of structure

$$=/\!\!\!\diagdown G^1{}_{)m}$$

wherein [binding] bonding is achieved via the terminal carbon atoms; or

iv) together form a bridge of structure

$$\begin{array}{c} T^1 \\ \diagdown\!\!\!= \\ T^1 \\ \diagup \\ T^1 \!=\! T^1 \end{array}$$

wherein one or two ring members T^1 are N and the others are CH, and

[binding] bonding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1 – 4; and

G^1 is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- phenyl lower alkoxycarbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;

- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- $-OCOR^6$;
- $-COR^6$;
- $-CO_2R^6$;
- $-CON(R^6)_2$;
- $-CH_2OR^3$;
- $-NO_2$;
- $-CN$;
- amidino;
- guanidino;
- sulfo;
- $-B(OH)2$;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- $-OCO_2R^3$;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;

- -S(O)$_p$(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)$_p$(optionally substituted heteroarylalkyl);
- -CHO;
- -OCON(R^6)$_2$;
- -NR^{3}CO$_2$R^6 ;
- -NR^{3}CON(R^6)$_2$

R^3 is H or lower alkyl;

R^6 is independently selected from the group consisting of

- H;
- alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

R^4 is H, halogen, or lower alkyl;

p is 0, 1, or 2;

X is selected from the group consisting of O, S, and NH;

Y is selected from the group consisting of

- -(CR$^4{}_2$)$_n$-S(O)$_p$-(5-membered heteroaryl)-(CR$^4{}_2$)$_s$-;
- -(CR$^4{}_2$)$_n$-C(G^2)(R^4)-(CR$^4{}_2$)$_s$- ;
  wherein
    n and s are each independently 0 or an integer of 1 – 2; and
    G^2 is selected from the group consisting of -CN, -CO$_2$R^3, -CON(R^6)$_2$, and
      –CH$_2$N(R^6)$_2$;
- -O-CH$_2$- ;
- -S(O)- ;
- -S(O)$_2$- ;

68

- $-SCH_2-$;
- $-S(O)CH_2-$;
- $-S(O)_2CH_2-$;
- $-CH_2S(O)-$; and
- $-CH_2S(O)_2-$

A and D independently represent N or CH;

B and E independently represent N or CH;

L represents N or CH;

with the provisos that

a) the total number of N atoms in the ring containing A, B, D, E, and L is 1, 2, or 3; and

b) when L represents CH, at least one of A and D is an N atom;

q is 0, 1, or 2;

G^3 is selected from the group consisting of

- lower alkyl;
- $-NR^3COR^6$;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- $-OCOR^6$;
- $-COR^6$;
- $-CO_2R^6$;
- $-CH_2OR^3$;
- $-CON(R^6)_2$;
- $-S(O)_2N(R^6)_2$;

- $-NO_2$;
- $-CN$;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p$(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p$(optionally substituted heteroarylalkyl);
- $-OCON(R^6)_2$;
- $-NR^3CO_2R^6$;
- $-NR^3CON(R^6)_2$;

J is a ring selected from the group consisting of

- aryl;
- pyridyl; and
- cycloalkyl;

q' represents the number of substituents G^4 on ring J and is 0, 1, 2, 3, 4, or 5, and G^4 moieties are selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;

70

- N-lower alkylamino-substituted alkyl;

- N,N-di-lower alkylamino-substituted alkyl;

- N-lower alkanoylamino-substituted alkyl;

- hydroxy-substituted alkyl;

- cyano-substituted alkyl;

- carboxy-substituted alkyl;

- lower alkoxycarbonyl-substituted alkyl;

- phenyl lower alkoxycarbonyl-substituted alkyl;

- halogen-substituted alkylamino;

- amino-substituted alkylamino;

- N-lower alkylamino-substituted alkylamino;

- N,N-di-lower alkylamino-substituted alkylamino;

- N-lower alkanoylamino-substituted alkylamino;

- hydroxy-substituted alkylamino;

- cyano-substituted alkylamino;

- carboxy-substituted alkylamino;

- lower alkoxycarbonyl-substituted alkylamino;

- phenyl-lower alkoxycarbonyl-substituted alkylamino;

- $-OR^6$;

- $-SR^6$;

- $-S(O)R^6$;

- $-S(O)_2R^6$;

- halogenated lower alkoxy;

- halogenated lower alkylthio;

- halogenated lower alkylsulfonyl;

- $-OCOR^6$;

- $-COR^6$;

- $-CO_2R^6$;

- $-CON(R^6)_2$;

- $-CH_2OR^3$;

- $-NO_2$;

- -CN;

- amidino;

- guanidino;

- sulfo;

- -B(OH)2 ;

- optionally substituted aryl;

- optionally substituted heteroaryl;

- optionally substituted saturated heterocyclyl;

- optionally substituted partially unsaturated heterocyclyl;

- -OCO$_2$R^3;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- -S(O)$_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- -S(O)$_p$(optionally substituted heteroarylalkyl);

- -CHO;

- -OCON(R^6)$_2$;

- -NR^{3}CO$_2$R^6 ;

- -NR^{3}CON(R^6)$_2$

- fused ring-forming bridges attached to and connecting adjacent positions of ring J, said bridges having the structures:

a)

$$\begin{array}{c} T^2 \\ \| \\ T^3 \diagdown \diagup T^2 \end{array}$$

wherein

each T^2 independently represents N, CH, or CG^4;

T^3 represents S, O, CR^{4}G^4, C(R^4)$_2$, or NR^3; and

[binding] bonding to ring J is achieved via terminal atoms T^2 and T^3;

b)

$$T^2 \diagup\diagup T^2 \quad | \quad T^2 \diagdown T^2 \diagup\diagup T^2$$
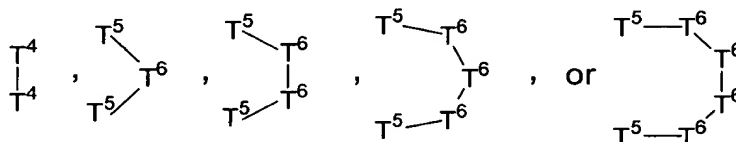
wherein

each T^2 independently represents N, CH, or CG^4;

with the proviso that a maximum of two bridge atoms T^2 may be N ;

and

[binding] <u>bonding</u> to ring J is achieved via terminal atoms T^2; and

c)

$$T^4 \atop T^4 \qquad , \qquad T^5 \diagdown T^6 \atop T^5 \diagup \qquad , \qquad T^5 \diagdown T^6 \atop T^5 \diagup T^6 \qquad , \qquad T^5-T^4 \diagdown T^6 \atop T^5-T^6 \diagup \qquad , \text{ or } \qquad T^5-T^6 \diagdown T^6 \atop T^5-T^6$$

wherein

each T^4, T^5, and T^6 independently represents O, S, CR^4G^4, $C(R^4)_2$, or NR^3; and

[binding] <u>bonding</u> to ring J is achieved via terminal atoms T^4 or T^5 ;

with the provisos that:

i) when one T^4 is O, S, or NR^3, the other T^4 is CR^4G^4 or $C(R^4)_2$;

ii) a bridge comprising T^5 and T^6 atoms may contain a maximum of two heteroatoms O, S, or N; and

iii) in a bridge comprising T^5 and T^6 atoms, when one T^5 group and one T^6 group are O atoms, or two T^6 groups are O atoms, said O atoms are separated by at least one carbon atom;
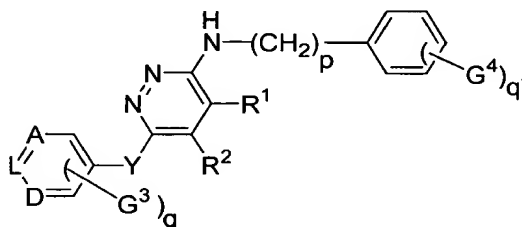
and with the further provisos that:

- in G^1, G^2, G^3, and G^4, when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a [N-containing] heterocycle of 5 – 7 ring atoms; and

73

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, $-CO_2R^3$, $-CHO$, $-CH_2OR^3$, $-OCO_2R^3$, $-CON(R^6)_2$, $-OCO\ N(R^6)_2$, $-NR^3CON(R^6)_2$, nitro, amidino, guanidino, mercapto, sulfo, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

2. (amended) A compound having the [generalized] structural formula

wherein

R^1 and R^2 :

i) together form a bridge of structure

wherein [binding] bonding is achieved via the terminal carbon atoms; or

ii) together form a bridge of structure

wherein one of the ring members T^1 is N and the others are CH, and [binding]

bonding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1 − 2; and

G^1 is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- $-OCOR^6$;
- $-COR^6$;
- $-CO_2R^6$;
- $-CON(R^6)_2$;
- $-NO_2$;
- $-CN$;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p$(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p$(optionally substituted heteroarylalkyl);

R^3 is H or lower alkyl;

R^6 is independently selected from the group consisting of

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

p is 0 or 1;

Y is selected from the group consisting of

- $-(CH_2)_n-S(O)_p-(5\text{-membered heteroaryl})-(CH_2)_s-$;
- $-(CH_2)_n-C(G^2)(H)-(CH_2)_s-$;

    wherein

    n and s are each independently 0 or 1; and

    G^2 is selected from the group consisting of $-CN$, $-CO_2R^3$, $-CON(R^6)_2$, and $-CH_2N(R^6)_2$;

- $-O-CH_2-$;
- $-S(O)-$;
- $-S(O)_2-$;
- $-SCH_2-$;
- $-S(O)CH_2-$;
- $-S(O)_2CH_2-$;
- $-CH_2S(O)-$; and
- $-CH_2S(O)_2-$

A and D independently represent N or CH;

L represents N or CH;

with the provisos that

a) the total number of N atoms in the ring containing A, D, and L is 1 or 2; and

b) when L represents CH, at least one of A and D is an N atom;

76

q is 0, 1, or 2;

G^3 is selected from the group consisting of

- lower alkyl;
- $-NR^3COR^6$;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- $-CO_2R^6$;
- $-CON(R^6)_2$;
- $-S(O)_2N(R^6)_2$;
- $-CN$;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p$(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p$(optionally substituted heteroarylalkyl);

q' represents the number of substituents G^4 on the phenyl ring and is 0, 1, 2, or 3; and

G^4 moieties are selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- alkyl;
- halogen-substituted alkyl;
- hydroxy-substituted alkyl;
- carboxy-substituted alkyl;

- lower alkoxycarbonyl-substituted alkyl;

- amino-substituted alkylamino;

- N-lower alkylamino-substituted alkylamino;

- N,N-di-lower alkylamino-substituted alkylamino;

- N-lower alkanoylamino-substituted alkylamino;

- hydroxy-substituted alkylamino;

- carboxy-substituted alkylamino;

- lower alkoxycarbonyl-substituted alkylamino;

- phenyl-lower alkoxycarbonyl-substituted alkylamino;

- $-OR^6$;

- $-SR^6$;

- $-S(O)R^6$;

- $-S(O)_2R^6$;

- halogenated lower alkoxy;

- halogenated lower alkylthio;

- halogenated lower alkylsulfonyl;

- $-OCOR^6$;

- $-COR^6$;

- $-CO_2R^6$;

- $-CON(R^6)_2$;

- $-CH_2OR^3$;

- $-NO_2$;

- $-CN$;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:

78

a)

$$T^2\\\backslash\!\!\backslash T^2\diagup_{T^3}^{T^2}$$

wherein

each T^2 independently represents N, CH, or CG^4;

T^3 represents S, O, CHG^4, CH_2, or NR^3; and

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms T^2 and T^3;

b)

$$T^2\diagdown\!\!\diagdown T^2\diagup T^2 |_{T^2}$$

wherein

each T^2 independently represents N, CH, or CG^4;

with the proviso that a maximum of two bridge atoms T^2 may be N ; and

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms T^2;

and

c)

$$T^5\diagdown\diagup^{T^6}_{T^5} \quad \text{or} \quad T^5\diagdown T^6 |^{T^6}_{T^5}$$

wherein

each T^5, and T^6 independently represents O, S, CHG^4, CH_2, or NR^3; and

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms T^5 ;

with the provisos that:

   i) a bridge comprising T^5 and T^6 atoms may contain a maximum of two heteroatoms O, S, or N; and

79

ii) in a bridge comprising T^5 and T^6 atoms, when one T^5 group and one T^6 group are O atoms, or two T^6 groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G^1, G^2, G^3, and G^4, when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a [N-containing] heterocycle of 5 – 7 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, $-CO_2R^3$, $-CH_2OR^3$, $-OCO_2R^3$, -$CON(R^6)_2$, $-OCO\,N(R^6)_2$, $-NR^3CON(R^6)_2$, nitro, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

3. (amended) A compound having the [generalized] structural formula

wherein
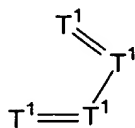
R^1 and R^2 :

i) together form a bridge of structure

wherein [binding] bonding is achieved via the terminal carbon atoms, and any group G^1 is located on a non-terminal atom of the bridge; or

ii) together form a bridge of structure

$$T^1 = T^1 - T^1 - T^1 = T^1$$

wherein one of the ring members T^1 is N and the others are CH, and [binding]

<u>bonding</u> is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1 – 2; and

G^1 is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;

- $-NR^3COR^6$;

- halogen;

- $-OR^6$ wherein R6 represents lower alkyl;

- $-NO_2$;

- optionally substituted heteroaryloxy;

- optionally substituted heteroarylalkyloxy;

R^3 is H or lower alkyl;

R^6 is independently selected from the group consisting of

- H;

- lower alkyl;

- optionally substituted aryl;

- optionally substituted aryl lower alkyl; and

p is 0 or 1;

Y is selected from the group consisting of

- $-S(O)_p$-(5-membered heteroaryl)-;

- $-C(CN)(H)-$;

- -O-CH$_2$- ;
- -S(O)- ; and
- -S(O)$_2$- ;

q is 0 or 1;

G^3 is selected from the group consisting of

- lower alkyl;
- -NR^{3}COR^6;
- -CO$_2$R^6;
- -CON(R^6)$_2$;
- -S(O)$_2$N(R^6)$_2$;

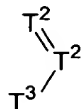q' represents the number of substituents G^4 on the phenyl ring and is 0, 1, 2, or 3; and

G^4 moieties are selected from the group consisting of

- -N(R^6)$_2$;
- halogen;
- lower alkyl;
- halogen-substituted lower alkyl;
- -OR^6;
- -SR^6;
- -S(O)R^6;
- -S(O)$_2$R^6;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- -OCOR^6;
- -COR^6;
- -CO$_2$R^6;
- -CON(R^6)$_2$;

- $-CH_2OR^3$;

- $-NO_2$;

- $-CN$;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:
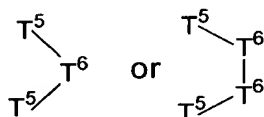
a)

wherein

each T^2 independently represents N, CH, or CG^4;

T^3 represents S, O, CHG^4, CH_2, or NR^3; and

[binding] bonding to the phenyl ring is achieved via terminal atoms T^2 and T^3;

b)

wherein

each T^5, and T^6 independently represents O, S, CHG^4, CH_2, or NR^3; and

[binding] bonding to the phenyl ring is achieved via terminal atoms T^5

;

with the provisos that:

    i) a bridge comprising T^5 and T^6 atoms may contain a maximum of two heteroatoms O, S, or N; and

ii) in a bridge comprising T^5 and T^6 atoms, when one T^5 group and one T^6 group are O atoms, or two T^6 groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

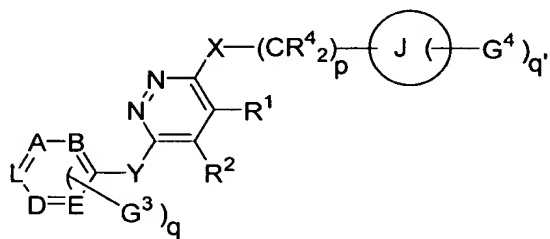- in G^1, G^2, G^3, and G^4, when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a [N-containing] heterocycle of 5 – 6 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, $-CO_2R^3$, $-CON(R^6)_2$, nitro, and cyano;

or a pharmaceutically acceptable salt or prodrug thereof.

4. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

5. (Amended) A method of treating a mammal having a condition [characterized by abnormal angiogenesis or hyperpermiability processes,] of tumor growth, retinopathy, rheumatoid arthritis, psoriasis, or a bullous disorder associated with subepidermal blister formation, comprising administering to said mammal an amount of a compound of claim 1 which is effective to treat said condition.

6. (cancelled) The method of claim 5, wherein said condition is tumor growth; retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, and age-related macular degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.
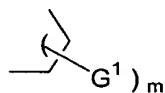
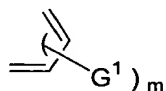7. (amended) A compound having the [generalized] structural formula

wherein

R^1 and R^2 :

i)   independently represent H or lower alkyl;
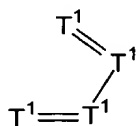
ii) together form a bridge of structure

wherein [binding] bonding is achieved via the terminal carbon atoms;

iii) together form a bridge of structure

wherein [binding] bonding is achieved via the terminal carbon atoms; or

iv) together form a bridge of structure

wherein one or two ring members T^1 are N and the others are CH, and

[binding] bonding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1 − 4; and

G^1 is a substituent independently selected from the group consisting of

• $-N(R^6)_2$;

85

- $-NR^3COR^6$;
- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- phenyl lower alkoxycarbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- halogenated lower alkoxy;

- halogenated lower alkylthio;

- halogenated lower alkylsulfonyl;

- $-OCOR^6$;

- $-COR^6$;

- $-CO_2R^6$;

- $-CON(R^6)_2$;

- $-CH_2OR^3$;

- $-NO_2$;

- $-CN$;

- amidino;

- guanidino;

- sulfo;

- $-B(OH)2$;

- optionally substituted aryl;

- optionally substituted heteroaryl;

- optionally substituted saturated heterocyclyl;

- optionally substituted partially unsaturated heterocyclyl;

- $-OCO_2R^3$;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

- $-CHO$;

- $-OCON(R^6)_2$;

- $-NR^3CO_2R^6$;

- $-NR^3CON(R^6)_2$

R^3 is H or lower alkyl;

R^6 is independently selected from the group consisting of

87

- H;
- alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

R^4 is H, halogen, or lower alkyl;

p is 0, 1, or 2;

X is selected from the group consisting of O, S, and NH;

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH or OAcyl;
- $-CH_2-O-$;
- $-CH_2-S-$;
- $-CH_2-NH-$;
- $-O-$;
- $-S-$;
- $-NH-$;
- $-(CR^4{}_2)_n-S(O)_p-(5\text{-membered heteroaryl})-(CR^4{}_2)_s-$;
- $-(CR^4{}_2)_n-C(G^2)(R^4)-(CR^4{}_2)_s-$;
  wherein

    n and s are each independently 0 or an integer of $1 - 2$; and

    G^2 is selected from the group consisting of -CN, $-CO_2R^3$, $-CON(R^6)_2$, and $-CH_2N(R^6)_2$;

- $-O-CH_2-$;
- $-S(O)-$;
- $-S(O)_2-$;
- $-SCH_2-$;
- $-S(O)CH_2-$;
- $-S(O)_2CH_2-$;

- $-CH_2S(O)-$; and

- $-CH_2S(O)_2-$

A and D independently represent N or CH;

B and E independently represent N or CH;

L represents N or CH;

    with the provisos that

    a) the total number of N atoms in the ring containing A, B, D, E, and L is 1, 2, or 3;

       and

    b) when L represents CH, at least one of A and D is an N atom;

q is 0, 1, or 2;

G^3 is selected from the group consisting of

- $-NR^3COR^6$;

- carboxy-substituted alkyl;

- lower alkoxycarbonyl-substituted alkyl;

- $-OR^6$;

- $-SR^6$;

- $-S(O)R^6$;

- $-S(O)_2R^6$;

- $-OCOR^6$;

- $-COR^6$;

- $-CO_2R^6$;

- $-CH_2OR^3$;

- $-CON(R^6)_2$;

- $-S(O)_2N(R^6)_2$;

- $-NO_2$;

- $-CN$;

- optionally substituted aryl;

- optionally substituted heteroaryl;

- optionally substituted saturated heterocyclyl;

- optionally substituted partially unsaturated heterocyclyl;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

- $-OCON(R^6)_2$;

- $-NR^3CO_2R^6$;

- $-NR^3CON(R^6)_2$;

J is a ring selected from the group consisting of
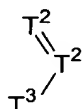
- aryl;

- pyridyl; and

- cycloalkyl;

q' represents the number of substituents G^4 on ring J and is 0, 1, 2, 3, 4, or 5, and G^4 moieties are selected from the group consisting of

- $-N(R^6)_2$;

- $-NR^3COR^6$;

- halogen;

- alkyl;

- cycloalkyl;

- lower alkenyl;

- lower cycloalkenyl;

- halogen-substituted alkyl;

- amino-substituted alkyl;

- N-lower alkylamino-substituted alkyl;

- N,N-di-lower alkylamino-substituted alkyl;

- N-lower alkanoylamino-substituted alkyl;

- hydroxy-substituted alkyl;

- cyano-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- phenyl lower alkoxycarbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- halogenated lower alkoxy;
- halogenated lower alkylthio;
- halogenated lower alkylsulfonyl;
- $-OCOR^6$;
- $-COR^6$;
- $-CO_2R^6$;
- $-CON(R^6)_2$;
- $-CH_2OR^3$;
- $-NO_2$;
- $-CN$;
- amidino;
- guanidino;
- sulfo;

- $-B(OH)2$;

- optionally substituted aryl;

- optionally substituted heteroaryl;

- optionally substituted saturated heterocyclyl;

- optionally substituted partially unsaturated heterocyclyl;

- $-OCO_2R^3$;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

- $-CHO$;

- $-OCON(R^6)_2$;

- $-NR^3CO_2R^6$;

- $-NR^3CON(R^6)_2$

- fused ring-forming bridges attached to and connecting adjacent positions of
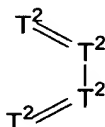
    ring J, said bridges having the structures:

a)

wherein

   each T^2 independently represents N, CH, or CG^4;

   T^3 represents S, O, CR^4G^4, $C(R^4)_2$, or NR^3; and

   [binding] bonding to ring J is achieved via terminal atoms T^2 and T^3;
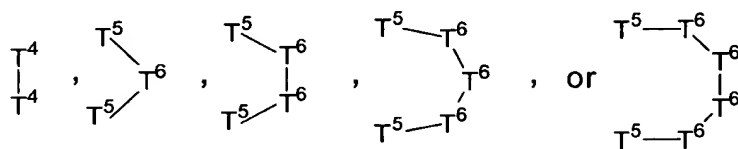
b)

wherein

   each T^2 independently represents N, CH, or CG^4;

with the proviso that a maximum of two bridge atoms T^2 may be N ;

and

[binding] <u>bonding</u> to ring J is achieved via terminal atoms T^2; and

c)

wherein

each T^4, T^5, and T^6 independently represents O, S, CR^4G^4, $C(R^4)_2$, or NR^3; and

[binding] <u>bonding</u> to ring J is achieved via terminal atoms T^4 or T^5 ;
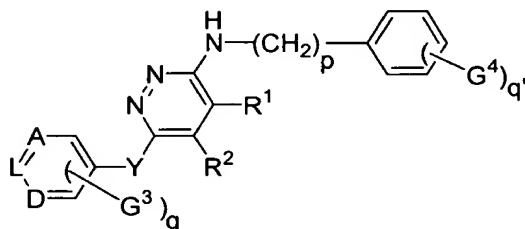
with the provisos that:

   i) when one T^4 is O, S, or NR^3, the other T^4 is CR^4G^4 or $C(R^4)_2$;

   ii) a bridge comprising T^5 and T^6 atoms may contain a maximum of two heteroatoms O, S, or N; and

   iii) in a bridge comprising T^5 and T^6 atoms, when one T^5 group and one T^6 group are O atoms, or two T^6 groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G^1, G^2, G^3, and G^4, when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a [N-containing] heterocycle of 5 – 7 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, $-CO_2R^3$, -CHO, $-CH_2OR^3$, -

OCO_2R^3, $-CON(R^6)_2$, $-OCO\ N(R^6)_2$, $-NR^3CON(R^6)_2$, nitro, amidino, guanidino,

mercapto, sulfo, and cyano;

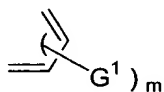or a pharmaceutically acceptable salt or prodrug thereof.

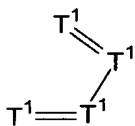8. (amended) A compound having the [generalized] structural formula

wherein

R^1 and R^2 :

   i)   together form a bridge of structure

        wherein [binding] <u>bonding</u> is achieved via the terminal carbon atoms; or

   ii) together form a bridge of structure

        wherein one of the ring members T^1 is N and the others are CH, and [binding]

         <u>bonding</u> is achieved via the terminal atoms; and

        wherein

        m is 0 or an integer 1 – 2; and

G^1 is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- alkyl;

- amino-substituted alkylamino;

- N-lower alkylamino-substituted alkylamino;

- N,N-di-lower alkylamino-substituted alkylamino;

- N-lower alkanoylamino-substituted alkylamino;

- hydroxy-substituted alkylamino;

- carboxy-substituted alkylamino;

- lower alkoxycarbonyl-substituted alkylamino;

- $-OR^6$;

- $-SR^6$;

- $-S(O)R^6$;

- $-S(O)_2R^6$;

- halogenated lower alkoxy;

- halogenated lower alkylthio;

- halogenated lower alkylsulfonyl;

- $-OCOR^6$;

- $-COR^6$;

- $-CO_2R^6$;

- $-CON(R^6)_2$;

- $-NO_2$;

- $-CN$;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

R^3 is H or lower alkyl;

R^6 is independently selected from the group consisting of

- H;

- lower alkyl;

95

- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

p is 0 or 1;

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH or OAcyl;
- $-CH_2-O-$;
- $-CH_2-S-$;
- $-CH_2-NH-$;
- $-O-$;
- $-S-$;
- $-NH-$;
- $-(CH_2)_n-S(O)_p-(5\text{-membered heteroaryl})-(CH_2)_s-$;
- $-(CH_2)_n-C(G^2)(H)-(CH_2)_s-$;

  wherein

  n and s are each independently 0 or 1; and

  G^2 is selected from the group consisting of $-CN$, $-CO_2R^3$, $-CON(R^6)_2$, and $-CH_2N(R^6)_2$;

- $-O-CH_2-$;
- $-S(O)-$;
- $-S(O)_2-$;
- $-SCH_2-$;
- $-S(O)CH_2-$;
- $-S(O)_2CH_2-$;
- $-CH_2S(O)-$; and
- $-CH_2S(O)_2-$

A and D independently represent N or CH;

L represents N or CH;

  with the provisos that

a) the total number of N atoms in the ring containing A, D, and L is 1 or 2; and

b) when L represents CH, at least one of A and D is an N atom;

q is 0, 1, or 2;

G^3 is selected from the group consisting of

- $-NR^3COR^6$;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- $-CO_2R^6$;
- $-CON(R^6)_2$;
- $-S(O)_2N(R^6)_2$;
- $-CN$;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p$(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p$(optionally substituted heteroarylalkyl);

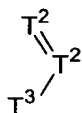q' represents the number of substituents G^4 on the phenyl ring and is 0, 1, 2, or 3; and

G^4 moieties are selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- alkyl;
- halogen-substituted alkyl;

97

- hydroxy-substituted alkyl;

- carboxy-substituted alkyl;

- lower alkoxycarbonyl-substituted alkyl;

- amino-substituted alkylamino;

- N-lower alkylamino-substituted alkylamino;

- N,N-di-lower alkylamino-substituted alkylamino;

- N-lower alkanoylamino-substituted alkylamino;

- hydroxy-substituted alkylamino;

- carboxy-substituted alkylamino;

- lower alkoxycarbonyl-substituted alkylamino;

- phenyl-lower alkoxycarbonyl-substituted alkylamino;

- $-OR^6$;

- $-SR^6$;

- $-S(O)R^6$;

- $-S(O)_2R^6$;

- halogenated lower alkoxy;

- halogenated lower alkylthio;

- halogenated lower alkylsulfonyl;

- $-OCOR^6$;

- $-COR^6$;

- $-CO_2R^6$;

- $-CON(R^6)_2$;

- $-CH_2OR^3$;

- $-NO_2$;

- $-CN$;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:
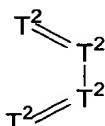
a)

$$T^2 \diagdown T^2 \diagup T^3$$

wherein

each T^2 independently represents N, CH, or CG^4;

T^3 represents S, O, CHG^4, $C(H)_2$, or NR^3; and

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms T^2 and T^3;

b)

$$T^2 \diagdown T^2 \;/\; T^2 \diagup T^2$$

wherein

each T^2 independently represents N, CH, or CG^4;
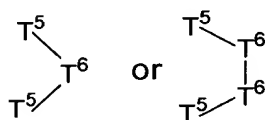
with the proviso that a maximum of two bridge atoms T^2 may be N ;

    and

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms T^2;

and

c)

$$T^5 \diagdown T^6 \diagup T^5 \qquad \text{or} \qquad T^5 \diagdown T^6 \;/\; T^5 \diagup T^6$$

wherein

each T^5, and T^6 independently represents O, S, CHG^4, $C(H)_2$, or NR^3;

    and

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms T^5 ;
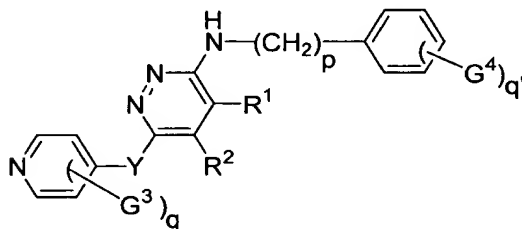
with the provisos that:

i) a bridge comprising T^5 and T^6 atoms may contain a maximum of two heteroatoms O, S, or N; and

ii) in a bridge comprising T^5 and T^6 atoms, when one T^5 group and one T^6 group are O atoms, or two T^6 groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G^1, G^2, G^3, and G^4, when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a [N-containing] heterocycle of 5 – 7 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, $-CO_2R^3$, $-CH_2OR^3$, $-OCO_2R^3$, $-CON(R^6)_2$, $-OCO\ N(R^6)_2$, $-NR^3CON(R^6)_2$, nitro, and cyano;

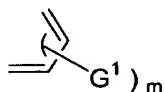or a pharmaceutically acceptable salt or prodrug thereof.

9. (amended) A compound having the [generalized] structural formula
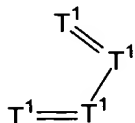

wherein

R^1 and R^2 :

    i)   together form a bridge of structure

wherein [binding] bonding is achieved via the terminal carbon atoms, and any

group G^1 is located on a non-terminal atom of the bridge; or

ii) together form a bridge of structure

$$T^1 \diagdown \atop T^1 = T^1 \diagup T^1$$

wherein one of the ring members T^1 is N and the others are CH, and [binding]

bonding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1 – 2; and

G^1 is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- $-OR^6$ wherein R6 represents lower alkyl;
- $-NO_2$;
- optionally substituted heteroaryloxy;
- optionally substituted heteroarylalkyloxy;

R^3 is H or lower alkyl;

R^6 is independently selected from the group consisting of

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

p is 0 or 1;

101

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH;
- $-CH_2-O-$;
- $-S-$;
- $-NH-$;
- $-S(O)_p-(5\text{-membered heteroaryl})-$;
- $-C(CN)(H)-$;
- $-O-CH_2-$;
- $-S(O)-$; and
- $-S(O)_2-$;

q is 0 or 1;

G^3 is selected from the group consisting of

- $-NR^3COR^6$;
- $-CO_2R^6$;
- $-CON(R^6)_2$;
- $-S(O)_2N(R^6)_2$;

q' represents the number of substituents G^4 on the phenyl ring and is 0, 1, 2, or 3; and

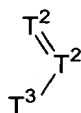G^4 moieties are selected from the group consisting of

- $-N(R^6)_2$;
- halogen;
- lower alkyl;
- halogen-substituted lower alkyl;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- halogenated lower alkoxy;

- halogenated lower alkylthio;

- halogenated lower alkylsulfonyl;

- $-OCOR^6$;

- $-COR^6$;

- $-CO_2R^6$;

- $-CON(R^6)_2$;

- $-CH_2OR^3$;

- $-NO_2$;

- $-CN$;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:
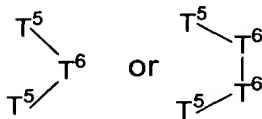
a)

wherein

each T^2 independently represents N, CH, or CG^4;

T^3 represents S, O, CHG^4, CH_2, or NR^3; and

[binding] bonding to the phenyl ring is achieved via terminal atoms T^2 and T^3;

b)

wherein

each T^5, and T^6 independently represents O, S, CHG^4, CH_2, or NR^3; and

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms

T^5 ;

with the provisos that:

i) a bridge comprising T^5 and T^6 atoms may contain a maximum of two heteroatoms O, S, or N; and

ii) in a bridge comprising T^5 and T^6 atoms, when one T^5 group and one T^6 group are O atoms, or two T^6 groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G^1, G^2, G^3, and G^4, when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a [N-containing] heterocycle of 5 – 6 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, $-CO_2R^3$, $-CON(R^6)_2$, nitro, and cyano;
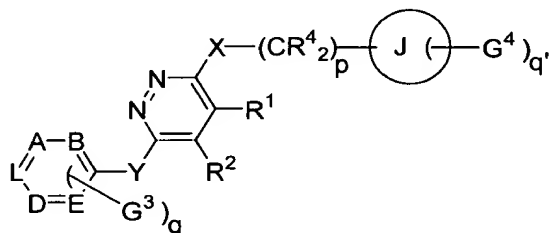
or a pharmaceutically acceptable salt or prodrug thereof.

10. A pharmaceutical composition comprising a compound of claim 7 and a pharmaceutically acceptable carrier.

11. (Amended) A method of treating a mammal having a condition [characterized by abnormal angiogenesis or hyperpermiability processes,] <u>of tumor growth, retinopathy, rheumatoid arthritis, psoriasis, or a bullous disorder associated with subepidermal blister formation,</u> comprising administering to said mammal an amount of a compound of claim 7 which is effective to treat said condition.

12. (cancelled) The method of claim 11, wherein said condition is tumor growth; retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, and age-related macular degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.
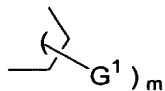
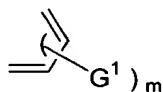13. (amended) A compound having the [generalized] structural formula

wherein

R^1 and R^2 :

    i)   independently represent H or lower alkyl;

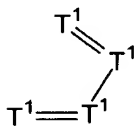   ii) together form a bridge of structure

        wherein [binding] bonding is achieved via the terminal carbon atoms;

    iii) together form a bridge of structure

        wherein [binding] bonding is achieved via the terminal carbon atoms; or

    iv) together form a bridge of structure

        wherein one or two ring members T^1 are N and the others are CH, and

        [binding] bonding is achieved via the terminal atoms; and

    wherein

105

m is 0 or an integer 1 − 4; and

G^1 is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- alkyl;
- cycloalkyl;
- lower alkenyl;
- lower cycloalkenyl;
- halogen-substituted alkyl;
- amino-substituted alkyl;
- N-lower alkylamino-substituted alkyl;
- N,N-di-lower alkylamino-substituted alkyl;
- N-lower alkanoylamino-substituted alkyl;
- hydroxy-substituted alkyl;
- cyano-substituted alkyl;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- phenyl lower alkoxycarbonyl-substituted alkyl;
- halogen-substituted alkylamino;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- cyano-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- phenyl-lower alkoxycarbonyl-substituted alkylamino;

- $-OR^6$;

- $-SR^6$;

- $-S(O)R^6$;

- $-S(O)_2R^6$;

- halogenated lower alkoxy;

- halogenated lower alkylthio;

- halogenated lower alkylsulfonyl;

- $-OCOR^6$;

- $-COR^6$;

- $-CO_2R^6$;

- $-CON(R^6)_2$;

- $-CH_2OR^3$;

- $-NO_2$;

- $-CN$;

- amidino;

- guanidino;

- sulfo;

- $-B(OH)2$;

- optionally substituted aryl;

- optionally substituted heteroaryl;

- optionally substituted saturated heterocyclyl;

- optionally substituted partially unsaturated heterocyclyl;

- $-OCO_2R^3$;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

- $-CHO$;

- $-OCON(R^6)_2$;

- $-NR^3CO_2R^6$;

- $-NR^3CON(R^6)_2$

R^3 is H or lower alkyl;

R^6 is independently selected from the group consisting of

- H;
- alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

R^4 is H, halogen, or lower alkyl;

p is 0, 1, or 2;

X is selected from the group consisting of O, S, and NH;

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH or OAcyl;
- $-CH_2-O-$;
- $-CH_2-S-$;
- $-CH_2-NH-$;
- $-O-$;
- $-S-$;
- $-NH-$;
- $-(CR^4_2)_n-S(O)_p-(5\text{-membered heteroaryl})-(CR^4_2)_s-$;
- $-(CR^4_2)_n-C(G^2)(R^4)-(CR^4_2)_s-$;
  wherein
    n and s are each independently 0 or an integer of 1 − 2; and
    G^2 is selected from the group consisting of -CN, $-CO_2R^3$, $-CON(R^6)_2$, and
      $-CH_2N(R^6)_2$;
- $-O-CH_2-$;
- $-S(O)-$;

108

- $-S(O)_2-$;
- $-SCH_2-$;
- $-S(O)CH_2-$;
- $-S(O)_2CH_2-$;
- $-CH_2S(O)-$; and
- $-CH_2S(O)_2-$

A and D independently represent N or CH;

B and E independently represent N or CH;

L represents N or CH;

with the provisos that

a) the total number of N atoms in the ring containing A, B, D, E, and L is 1, 2, or 3; and

b) when L represents CH, at least one of A and D is an N atom;

q is 0, 1, or 2;

G^3 is selected from the group consisting of

- lower alkyl;
- $-NR^3COR^6$;
- carboxy-substituted alkyl;
- lower alkoxycarbonyl-substituted alkyl;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- $-OCOR^6$;
- $-COR^6$;
- $-CO_2R^6$;
- $-CH_2OR^3$;
- $-CON(R^6)_2$;

- $-S(O)_2N(R^6)_2$;
- $-NO_2$;
- $-CN$;
- optionally substituted aryl;
- optionally substituted heteroaryl;
- optionally substituted saturated heterocyclyl;
- optionally substituted partially unsaturated heterocyclyl;
- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p$(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p$(optionally substituted heteroarylalkyl);
- $-OCON(R^6)_2$;
- $-NR^3CO_2R^6$;
- $-NR^3CON(R^6)_2$;
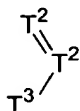
J is a ring selected from the group consisting of

- aryl;
- pyridyl; and
- cycloalkyl;

q' represents the number of substituents G^4 on ring J and is 0, 1, 2, 3, 4, or 5, and G^4 moieties are selected from the group consisting of

- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- $-S(O)_p$(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- $-S(O)_p$(optionally substituted heteroarylalkyl);
- $-CHO$;
- $-OCON(R^6)_2$;
- $-NR^3CO_2R^6$;

- $-NR^3CON(R^6)_2$
- fused ring-forming bridges attached to and connecting adjacent positions of ring J, said bridges having the structures:
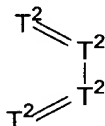
a)

$$\begin{array}{c} T^2 \\ \backslash\backslash \\ \quad T^2 \\ \diagup \\ T^3 \end{array}$$

wherein

each T^2 independently represents N, CH, or CG^4;

T^3 represents S, O, CR^4G^4, $C(R^4)_2$, or NR^3; and

[binding] bonding to ring J is achieved via terminal atoms T^2 and T^3;

b)

$$\begin{array}{c} T^2 \\ \diagdown \\ \quad T^2 \\ \quad | \\ T^2 \diagup T^2 \end{array}$$
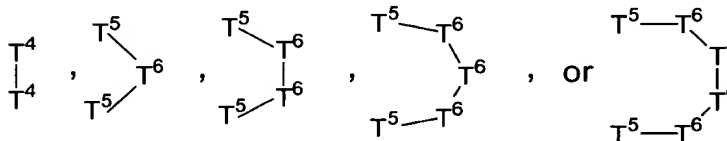
wherein

each T^2 independently represents N, CH, or CG^4;

with the proviso that a maximum of two bridge atoms T^2 may be N ; and

[binding] bonding to ring J is achieved via terminal atoms T^2; and

c)

$$\begin{array}{cccc} T^4 \quad T^5 & T^5 & T^5{-}T^6 & T^5{-}T^6 \\ | \quad \diagdown & \diagdown \quad T^6 & \diagdown & \diagdown \quad T^6 \\ | \quad T^6 & | & T^6 & | \\ T^4 \quad T^5 & T^5 {-} T^6 & T^5 {-} T^6 & T^6 \\ & & & T^5 {-} T^6 \end{array}$$, , , or

wherein

each T^4, T^5, and T^6 independently represents O, S, CR^4G^4, $C(R^4)_2$, or NR^3; and

[binding] bonding to ring J is achieved via terminal atoms T^4 or T^5 ;
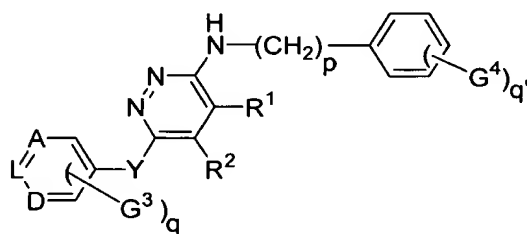
with the provisos that:

i) when one T^4 is O, S, or NR^3, the other T^4 is CR^4G^4 or $C(R^4)_2$;

111

ii) a bridge comprising T^5 and T^6 atoms may contain a maximum of two heteroatoms O, S, or N; and

iii) in a bridge comprising T^5 and T^6 atoms, when one T^5 is O, the other T^5 is S, CR^4G^4, $C(R^4)_2$ or NR^3 ;

iv) in a bridge comprising T^5 and T^6 atoms, when one T^5 group and one T^6 group are O atoms, or two T^6 groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G^1, G^2, G^3, and G^4, when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a [N-containing] heterocycle of 5 – 7 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 5 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, $-CO_2R^3$, -CHO, $-CH_2OR^3$, $-OCO_2R^3$, $-CON(R^6)_2$, $-OCO\ N(R^6)_2$, $-NR^3CON(R^6)_2$, nitro, amidino, guanidino, mercapto, sulfo, and cyano;

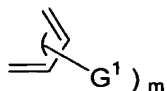or a pharmaceutically acceptable salt or prodrug thereof.

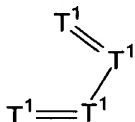14. (amended) A compound having the [generalized] structural formula

wherein

R^1 and R^2 :

i) together form a bridge of structure

$$=\!\!\!\!\begin{array}{c}\nwarrow \\ \diagup \\ G^1 \end{array}\!\!\!)_m$$

wherein [binding] <u>bonding</u> is achieved via the terminal carbon atoms; or

ii) together form a bridge of structure

$$\begin{array}{c} T^1 \\ \diagdown \\ T^1 \\ \diagup \\ T^1 = T^1 \end{array}$$

wherein one of the ring members T^1 is N and the others are CH, and [binding]

bonding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1 − 2; and

G^1 is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- alkyl;
- amino-substituted alkylamino;
- N-lower alkylamino-substituted alkylamino;
- N,N-di-lower alkylamino-substituted alkylamino;
- N-lower alkanoylamino-substituted alkylamino;
- hydroxy-substituted alkylamino;
- carboxy-substituted alkylamino;
- lower alkoxycarbonyl-substituted alkylamino;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
- $-S(O)_2R^6$;
- halogenated lower alkoxy;

113

- halogenated lower alkylthio;

- halogenated lower alkylsulfonyl;

- $-OCOR^6$;

- $-COR^6$;

- $-CO_2R^6$;

- $-CON(R^6)_2$;

- $-NO_2$;

- $-CN$;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

R^3 is H or lower alkyl;

R^6 is independently selected from the group consisting of

- H;

- lower alkyl;

- optionally substituted aryl;

- optionally substituted aryl lower alkyl; and

p is 0 or 1;

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH or OAcyl;

- $-CH_2-O-$;

- $-CH_2-S-$;

- $-CH_2-NH-$;

- $-O-$;

- $-S-$;

- -NH- ;
- $-(CH_2)_n-S(O)_p-(5\text{-membered heteroaryl})-(CH_2)_s-$;
- $-(CH_2)_n-C(G^2)(H)-(CH_2)_s-$;

  wherein

  n and s are each independently 0 or 1; and

  G^2 is selected from the group consisting of $-CN$, $-CO_2R^3$, $-CON(R^6)_2$, and $-CH_2N(R^6)_2$;

- $-O-CH_2-$;
- $-S(O)-$;
- $-S(O)_2-$;
- $-SCH_2-$;
- $-S(O)CH_2-$;
- $-S(O)_2CH_2-$;
- $-CH_2S(O)-$; and
- $-CH_2S(O)_2-$

A and D independently represent N or CH;

L represents N or CH;

  with the provisos that

  a) the total number of N atoms in the ring containing A, D, and L is 1 or 2; and

  b) when L represents CH, at least one of A and D is an N atom;

q is 0, 1, or 2;

G^3 is selected from the group consisting of

- lower alkyl;
- $-NR^3COR^6$;
- $-OR^6$;
- $-SR^6$;
- $-S(O)R^6$;
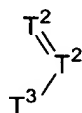- $-S(O)_2R^6$;
- $-CO_2R^6$;

115

- $-CON(R^6)_2$;

- $-S(O)_2N(R^6)_2$;

- -CN;

- optionally substituted aryl;

- optionally substituted heteroaryl;

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

q' represents the number of substituents G^4 on the phenyl ring and is 0, 1, 2, or 3;

and

G^4 moieties are selected from the group consisting of

- optionally substituted heteroarylalkyl;

- optionally substituted heteroaryloxy;

- $-S(O)_p$(optionally substituted heteroaryl);

- optionally substituted heteroarylalkyloxy;

- $-S(O)_p$(optionally substituted heteroarylalkyl);

- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:
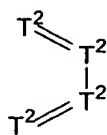
a)

$$T^2 \diagdown T^2 \diagup T^3$$

wherein

each T^2 independently represents N, CH, or CG^4;

T^3 represents S, O, CHG^4, $C(H)_2$, or NR^3; and

[binding] bonding to the phenyl ring is achieved via terminal atoms T^2 and T^3;

116

b)

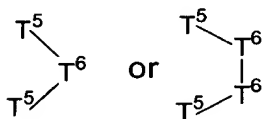$$T^2 \diagup T^2 \diagdown T^2 \diagup T^2$$

wherein

each T^2 independently represents N, CH, or CG^4;

with the proviso that a maximum of two bridge atoms T^2 may be N ;

and

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms T^2;

and

c)

$$T^5 \diagdown T^6 \diagup T^5 \quad \text{or} \quad T^5 \diagdown T^6 \diagup T^5$$

wherein

each T^5, and T^6 independently represents O, S, CHG^4, CH_2, or NR^3; and

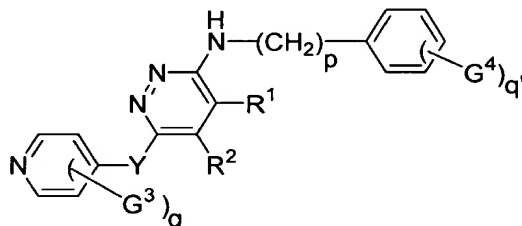[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms

T^5 ;

with the provisos that:

i) a bridge comprising T^5 and T^6 atoms may contain a maximum of two heteroatoms O, S, or N; and

ii) in a bridge comprising T^5 and T^6 atoms, when one T^5 is O, the other T^5 is S, CHG^4, CH_2 or NR^3 ;

iii) in a bridge comprising T^5 and T^6 atoms, when one T^5 group and one T^6 group are O atoms, or two T^6 groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G^1, G^2, G^3, and G^4, when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a [N-containing] heterocycle of 5 – 7 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, lower alkanoyloxy, $-CO_2R^3$, $-CH_2OR^3$, $-OCO_2R^3$, $-CON(R^6)_2$, $-OCO\ N(R^6)_2$, $-NR^3CON(R^6)_2$, nitro, and cyano;

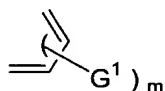or a pharmaceutically acceptable salt or prodrug thereof.

15. (amended) A compound having the [generalized] structural formula
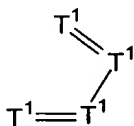

wherein

R^1 and R^2 :

   i)   together form a bridge of structure

       wherein [binding] <u>bonding</u> is achieved via the terminal carbon atoms, and any

        group G^1 is located on a non-terminal atom of the bridge; or

   ii) together form a bridge of structure

wherein one of the ring members T^1 is N and the others are CH, and [binding]

bonding is achieved via the terminal atoms; and

wherein

m is 0 or an integer 1 − 2; and

G^1 is a substituent independently selected from the group consisting of

- $-N(R^6)_2$;
- $-NR^3COR^6$;
- halogen;
- $-OR^6$ wherein R6 represents lower alkyl;
- $-NO_2$;
- optionally substituted heteroaryloxy;
- optionally substituted heteroarylalkyloxy;

R^3 is H or lower alkyl;

R^6 is independently selected from the group consisting of

- H;
- lower alkyl;
- optionally substituted aryl;
- optionally substituted aryl lower alkyl; and

p is 0 or 1;

Y is selected from the group consisting of

- lower alkylene, optionally substituted by OH;
- $-CH_2-O-$;
- $-S-$;
- $-NH-$;
- $-S(O)_p-(5$-membered heteroaryl)-;

119

- -C(CN)(H)- ;
- -O-CH$_2$- ;
- -S(O)- ; and
- -S(O)$_2$- ;

q is 0 or 1;

G^3 is selected from the group consisting of

- lower alkyl;
- -NR^{3}COR^6;
- -CO$_2$R^6;
- -CON(R^6)$_2$;
- -S(O)$_2$N(R^6)$_2$;

q' represents the number of substituents G^4 on the phenyl ring, and is 0, 1, 2, or 3;

and

G^4 moieties are selected from the group consisting of

- optionally substituted heteroarylalkyl;
- optionally substituted heteroaryloxy;
- -S(O)$_p$(optionally substituted heteroaryl);
- optionally substituted heteroarylalkyloxy;
- -S(O)$_p$(optionally substituted heteroarylalkyl);
- fused ring-forming bridges attached to and connecting adjacent positions of the phenyl ring, said bridges having the structures:
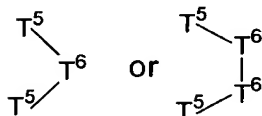
a)

wherein

each T^2 independently represents N, CH, or CG^4;

T^3 represents S, O, CHG^4, CH$_2$, or NR^3; and

120

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms T^2 and T^3;

b)

wherein

each T^5, and T^6 independently represents O, S, CHG^4, CH_2, or NR^3; and

[binding] <u>bonding</u> to the phenyl ring is achieved via terminal atoms T^5 ;

with the provisos that:

i) a bridge comprising T^5 and T^6 atoms may contain a maximum of two heteroatoms O, S, or N; and

ii) in a bridge comprising T^5 and T^6 atoms, when one T^5 is O, the other T^5 is S, CR^4G^4, $C(R^4)_2$ or NR^3 ;

iii) in a bridge comprising T^5 and T^6 atoms, when one T^5 group and one T^6 group are O atoms, or two T^6 groups are O atoms, said O atoms are separated by at least one carbon atom;

and with the further provisos that:

- in G^1, G^2, G^3, and G^4, when two groups R^6 are each alkyl and located on the same N atom they may be linked by a bond, an O, an S, or NR^3 to form a [N-containing] heterocycle of 5 – 6 ring atoms; and

- when an aryl, heteroaryl, or heterocyclyl ring is optionally substituted, that ring may bear up to 2 substituents which are independently selected from the group consisting of amino, mono-loweralkyl-substituted amino, di-loweralkyl-substituted amino, lower alkanoylamino, halogeno, lower alkyl, halogenated lower alkyl, hydroxy, lower alkoxy, lower alkylthio, halogenated lower alkoxy, halogenated lower alkylthio, $-CO_2R^3$, $-CON(R^6)_2$, nitro, and cyano;

121

or a pharmaceutically acceptable salt or prodrug thereof.

16. A pharmaceutical composition comprising a compound of claim 13 and a pharmaceutically acceptable carrier.

17. (Amended) A method of treating a mammal having a condition [characterized by abnormal angiogenesis or hyperpermiability processes,] of tumor growth, retinopathy, rheumatoid arthritis, psoriasis, or a bullous disorder associated with subepidermal blister formation, comprising administering to said mammal an amount of a compound of claim 13 which is effective to treat said condition.

18. (Cancelled) The method of claim 17, wherein said condition is tumor growth; retinopathy, including diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, and age-related macular degeneration; rheumatoid arthritis; psoriasis; or a bullous disorder associated with subepidermal blister formation, including bullous pemphigoid, erythema multiforme, and dermatitis herpetiformis.

19. (Amended) A compound selected from the group consisting of:
   a) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid methylamide;
   b) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid amide;
   c) 1-(4-chlorophenylamino)-4-(3-pyridylmethoxy)phthalazine;
   d) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic acid methylamide;
   e) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic acid amide;
   f) 4-[4-(3-Bromophenylamino)phthalazin-1-ylmethyl]-pyridin-2-yl carboxylic acid methylamide;
   g) 4-[4-(3-Bromophenylamino)phthalazin-1-ylmethyl]-pyridin-2-yl carboxylic acid amide;

h) 1-(4-chlorophenylamino)-4-[(2-phenyl-4-pyridyl)methyl]phthalazine;

i) 1-[4-(4-pyridyloxy)phenylamino]-4-(4-pyridylmethyl)phthalazine;

j) 1-(indan-5-ylamino)-4-(4-pyridylmethyl)phthalazine;

k) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid methylamide dihydrochloride;

l) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid methylamide dimethanesulfonate;

m) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin2-yl carboxylic acid amide dihydrochloride;

n) 4-[4-(4-Chlorophenylamino)phthalazin-1-ylmethyl]pyridin-2-yl carboxylic acid amide dimethanesulfonate;

o) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic acid amide dihydrochloride;

p) 4-[4-(4-Chlorophenylamino)phthalazin-1-yloxymethyl]pyridin-2-yl carboxylic acid amide dimethanesulfonate;

q) 1-(4-chlorophenylamino)-4-[5-(4-pyridyl)-1H-1,2,4-triazolyl-3-ylthio]phthalazine;

r) 1-(4-isopropylphenylamino)-4-[5-(4-pyridyl)-1H-1,2,4-triazolyl-3-ylthio]phthalazine

s) 1-(4-chlorophenylamino)-4-(4-pyridylsufonyl)phthalazine;

t) 1-(4-chlorophenylamino)-4-(4-pyridylsufinyl)phthalazine;

[u) 1-(4-chlorophenylamino)-4-(4-pyridylmethoxy)pyridazine;]

v) 1-(indan-5-ylamino)-4-(4-pyridylcyanomethyl)phthalazine; and

w) 1-(benzothiazol-6-ylamino)-4-(4-pyridylcyanomethyl)phthalazine.

20. (New) The method of claim 5, wherein said condition of retinopathy is diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, or age-related macular degeneration.

21. (New) The method of claim 5, wherein when said condition is a bullous disorder associated with subepidermal blister formation, it is bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis.

22. (New) The method of claim 11, wherein said condition of retinopathy is diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, or age-related macular degeneration.

23. (New) The method of claim 11, wherein when said condition is a bullous disorder associated with subepidermal blister formation, it is bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis.

24. (New) The method of claim 17, wherein said condition of retinopathy is diabetic retinopathy, ischemic retinal-vein occlusion, retinopathy of prematurity, or age-related macular degeneration.

25. (New) The method of claim 17, wherein when said condition is a bullous disorder associated with subepidermal blister formation, it is bullous pemphigoid, erythema multiforme, or dermatitis herpetiformis.